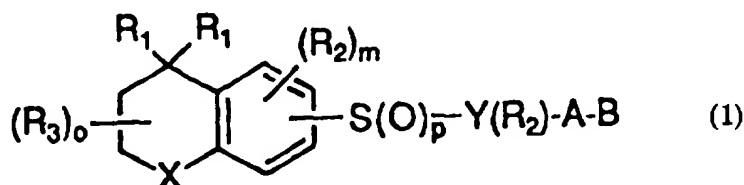




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>C07C 323/62, 317/44, C07D 213/80, 277/56, A61K 31/235, 31/455, 31/425</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/16422</b>  <b>(43) International Publication Date:</b> 9 May 1997 (09.05.97)
<b>(21) International Application Number:</b> PCT/US96/17295  <b>(22) International Filing Date:</b> 29 October 1996 (29.10.96)  <b>(30) Priority Data:</b> 08/552,965                      1 November 1995 (01.11.95)      US  <b>(71) Applicant:</b> ALLERGAN [US/US], 8301 Mars Drive, Waco, TX 76712 (US).  <b>(72) Inventors:</b> BEARD, Richard, L.; 2341 Azure Avenue, Newport Beach, CA 92660 (US). COLON, Diana, F.; 247 Veneto, Irvine, CA 92714 (US). CHANDRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US).  <b>(74) Agents:</b> BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (US).	<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

**(54) Title:** SULFIDES, SULFOXIDES AND SULFONES DISUBSTITUTED WITH A TETRAHYDRONAPHTHALENYL, CHROMANYL, THIOCHROMANYL OR TETRAHYDROQUINOLINYL AND SUBSTITUTED PHENYL OR HETEROARYL GROUP, HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY

**(57) Abstract**

Compounds of formula (1) wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or X is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> where n is an integer between 0 and 2; R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons; R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons; R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F; m is an integer having the value of 0-3; o is an integer having the value of 0-4; p is an integer having the value of 0-2; Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R<sub>2</sub> groups; A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO, CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or tri-lower alkylsilyl, where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R<sub>8</sub> is phenyl or lower alkylphenyl, R<sub>9</sub> and R<sub>10</sub> independently are hydrogen, an alkyl group of 1 to 10 carbons or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R<sub>11</sub> is lower alkyl, phenyl or lower alkylphenyl, R<sub>12</sub> is lower alkyl, and R<sub>13</sub> is divalent alkyl radical of 2-5 carbons, are selective agonists of RXR retinoid receptors.

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1       SULFIDES, SULFOXIDES AND SULFONES DISUBSTITUTED  
2       WITH A TETRAHYDRONAPHTHALENYL, CHROMANYL,  
3       THIOCHROMANYL OR TETRAHYDROQUINOLINYL AND  
4       SUBSTITUTED PHENYL OR HETEROARYL GROUP, HAVING  
5       RETINOID-LIKE BIOLOGICAL ACTIVITY

6       1.    Field of the Invention

7       The present invention relates to novel compounds having  
8   retinoid-like biological activity. More specifically, the present invention  
9   relates to sulfide, sulfoxide and sulfone compounds disubstituted with a  
10  tetrahydronaphthalenyl, chromanyl, thiochromanyl or  
11  tetrahydroquinoliny and substituted phenyl or heteroaryl group having  
12  retinoid-like biological activity.

13       2.   Background Art

14       Compounds which have retinoid-like activity are well known in  
15  the art, and are described in numerous United States and other patents  
16  and in scientific publications. It is generally known and accepted in the  
17  art that retinoid-like activity is useful for treating animals of the  
18  mammalian species, including humans, for curing or alleviating the  
19  symptoms and conditions of numerous diseases and conditions. In  
20  other words, it is generally accepted in the art that pharmaceutical  
21  compositions having a retinoid-like compound or compounds as the  
22  active ingredient are useful as regulators of cell proliferation and  
23  differentiation, and particularly as agents for treating skin-related  
24  diseases, including, actinic keratoses, arsenic keratoses, inflammatory  
25  and non-inflammatory acne, psoriasis, ichthyoses and other  
26  keratinization and hyperproliferative disorders of the skin, eczema,  
27  atopic dermatitis, Darriers disease, lichen planus, prevention and  
28  reversal of glucocorticoid damage (steroid atrophy), as a topical

1 anti-microbial, as skin anti-pigmentation agents and to treat and reverse  
2 the effects of age and photo damage to the skin. Retinoid compounds  
3 are also useful for the prevention and treatment of cancerous and  
4 precancerous conditions, including, premalignant and malignant  
5 hyperproliferative diseases such as cancers of the breast, skin, prostate,  
6 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral  
7 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,  
8 leukoplakias and papillomas of the mucous membranes and in the  
9 treatment of Kaposi's sarcoma. In addition, retinoid compounds can be  
10 used as agents to treat diseases of the eye, including, without limitation,  
11 proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and  
12 other corneopathies, as well as in the treatment and prevention of  
13 various cardiovascular diseases, including, without limitation, diseases  
14 associated with lipid metabolism such as dyslipidemias, prevention of  
15 post-angioplasty restenosis and in the treatment and prevention of  
16 diabetes and obesity and as an agent to increase the level of circulating  
17 tissue plasminogen activator (TPA). Other uses for retinoid compounds  
18 include the prevention and treatment of conditions and diseases  
19 associated with human papilloma virus (HPV), including warts and  
20 genital warts, various inflammatory diseases such as pulmonary fibrosis,  
21 ileitis, colitis and Krohn's disease, neurodegenerative diseases such as  
22 Alzheimer's disease, Parkinson's disease and stroke, improper pituitary  
23 function, including insufficient production of growth hormone,  
24 modulation of apoptosis, including both the induction of apoptosis and  
25 inhibition of T-Cell activated apoptosis, restoration of hair growth,  
26 including combination therapies with the present compounds and other  
27 agents such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
28 including use of the present compounds as immunosuppressants and

1 immunostimulants, modulation of organ transplant rejection and  
2 facilitation of wound healing, including modulation of chelosis.

3 United States Patent Nos. 4,740,519 (Shroot et al.), 4,826,969  
4 (Maignan et al.), 4,326,055 (Loeliger et al.), 5,130,335 (Chandraratna et  
5 al.), 5,037,825 (Klaus et al.), 5,231,113 (Chandraratna et al.), 5,324,840  
6 (Chandraratna), 5,344,959 (Chandraratna), 5,130,335 (Chandraratna et  
7 al.), Published European Patent Application Nos. 0 176 034 A (Wuest  
8 et al.), 0 350 846 A (Klaus et al.), 0 176 032 A (Frickel et al.), 0 176  
9 033 A (Frickel et al.), 0 253 302 A (Klaus et al.), 0 303 915 A (Bryce et  
10 al.), UK Patent Application GB 2190378 A (Klaus et al.), German  
11 Patent Application Nos. DE 3715955 A1 (Klaus et al.), DE 3602473 A1  
12 (Wuest et al., and the articles J. Amer. Acad. Derm. 15: 756 - 764  
13 (1986) (Sporn et al.), Chem. Pharm. Bull. 33: 404-407 (1985) (Shudo et  
14 al.), J. Med Chem. 1988 31, 2182 - 2192 (Kagechika et al.), Chemistry  
15 and Biology of Synthetic Retinoids CRC Press Inc. 1990 p 334 - 335,  
16 354 (Dawson et al.), describe or relate to compounds which include a  
17 tetrahydronaphthyl moiety and have retinoid-like or related biological  
18 activity. United States Patent No. 4,391,731 (Boller et al.) describes  
19 tetrahydronaphthalene derivatives which are useful in liquid crystal  
20 compositions.

21 United States Patent Nos. 4,980,369, 5,006,550, 5,015,658,  
22 5,045,551, 5,089,509, 5,134,159, 5,162,546, 5,234,926, 5,248,777,  
23 5,264,578, 5,272,156, 5,278,318, 5,324,744, 5,346,895, 5,346,915,  
24 5,348,972, 5,348,975, 5,380,877, 5,399,561, 5,407,937, (assigned to the  
25 same assignee as the present application) and patents and publications  
26 cited therein, describe or relate to chroman, thiochroman and  
27 1,2,3,4-tetrahydroquinoline derivatives which have retinoid-like  
28 biological activity. Still further, several co-pending applications and

1 recently issued patents which are assigned to the assignee of the present  
2 application, are directed to further compounds having retinoid-like  
3 activity.

4 It is now general knowledge in the art that two main types of  
5 retinoid receptors exist in mammals (and other organisms). The two  
6 main types or families of receptors respectively designated the RARs  
7 and RXRs. Within each type there are subtypes; in the RAR family  
8 the subtypes are designated RAR $\alpha$ , RAR $\beta$  and RAR $\gamma$ , in RXR the  
9 subtypes are: RXR $\alpha$ , RXR $\beta$  and RXR $\gamma$ . It has also been established in  
10 the art that the distribution of the two main retinoid receptor types,  
11 and of the several sub-types is not uniform in the various tissues and  
12 organs of mammalian organisms. Moreover, it is generally accepted in  
13 the art that many unwanted side effects of retinoids are mediated by  
14 one or more of the RAR receptor subtypes. Accordingly, among  
15 compounds having agonist-like activity at retinoid receptors, specificity  
16 or selectivity for one of the main types or families, and even specificity  
17 or selectivity for one or more subtypes within a family of receptors, is  
18 considered a desirable pharmacological property.

19 The present invention provides further compounds having  
20 retinoid-like biological activity and specifically compounds which are  
21 specific or highly selective agonists of RXR retinoid receptors in  
22 preference over RAR retinoid receptors.

### 23 SUMMARY OF THE INVENTION

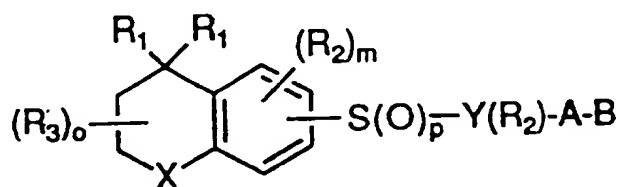
24 The present invention covers compounds of **Formula 1**

25

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Formula 1

- wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or  
 X is  $[C(R_1)_2]_n$  where n is an integer between 0 and 2;  
 R<sub>1</sub> is independently H or alkyl of 1 to 6 carbons;  
 R<sub>2</sub> is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF<sub>3</sub>,  
 fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6  
 carbons, or alkylthio of 1 to 6 carbons;  
 R<sub>3</sub> is hydrogen, lower alkyl of 1 to 6 carbons or F;  
 m is an integer having the value of 0 - 3;  
 o is an integer having the value of 0 - 4;  
 p is an integer having the value of 0 - 2;  
 Y is a phenyl or naphthyl group, or heteroaryl selected from a  
 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,  
 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolizyl, said phenyl and  
 heteroaryl groups being optionally substituted with one or two R<sub>2</sub>  
 groups;  
 A is (CH<sub>2</sub>)<sub>q</sub> where q is 0-5, lower branched chain alkyl having 3-6  
 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1  
 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds,  
 and  
 B is hydrogen, COOH or a pharmaceutically acceptable salt  
 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or tri-lower  
 alkylsilyl, where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1

1 to 5 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or  
2 (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a  
3 cycloalkyl group of 5 to 10 carbons, or  $R_8$  is phenyl or lower  
4 alkylphenyl,  $R_9$  and  $R_{10}$  independently are hydrogen, an alkyl group of 1  
5 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower  
6 alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower  
7 alkyl, and  $R_{13}$  is divalent alkyl radical of 2-5 carbons.

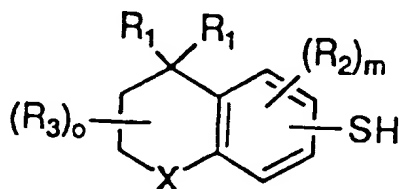
8 In a second aspect, this invention relates to the use of the  
9 compounds of **Formula 1** for the treatment of skin-related diseases,  
10 including, without limitation, actinic keratoses, arsenic keratoses,  
11 inflammatory and non-inflammatory acne, psoriasis, ichthyoses and  
12 other keratinization and hyperproliferative disorders of the skin,  
13 eczema, atopic dermatitis, Darriers disease, lichen planus, prevention  
14 and reversal of glucocorticoid damage (steroid atrophy), as a topical  
15 anti-microbial, as skin anti-pigmentation agents and to treat and reverse  
16 the effects of age and photo damage to the skin. The compounds are  
17 also useful for the prevention and treatment of cancerous and  
18 precancerous conditions, including, premalignant and malignant  
19 hyperproliferative diseases such as cancers of the breast, skin, prostate,  
20 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral  
21 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,  
22 leukoplakias and papillomas of the mucous membranes and in the  
23 treatment of Kaposi's sarcoma. In addition, the present compounds can  
24 be used as agents to treat diseases of the eye, including, without  
25 limitation, proliferative vitreoretinopathy (PVR), retinal detachment,  
26 dry eye and other corneopathies, as well as in the treatment and  
27 prevention of various cardiovascular diseases, including, without  
28 limitation, diseases associated with lipid metabolism such as



1 dyslipidemias, prevention of post-angioplasty restenosis and as an agent  
2 to increase the level of circulating tissue plasminogen activator (TPA).  
3 Other uses for the compounds of the present invention include the  
4 prevention and treatment of conditions and diseases associated with  
5 human papilloma virus (HPV), including warts and genital warts,  
6 various inflammatory diseases such as pulmonary fibrosis, ileitis, colitis  
7 and Krohn's disease, neurodegenerative diseases such as Alzheimer's  
8 disease, Parkinson's disease and stroke, improper pituitary function,  
9 including insufficient production of growth hormone, modulation of  
10 apoptosis, including both the induction of apoptosis and inhibition of  
11 T-Cell activated apoptosis, restoration of hair growth, including  
12 combination therapies with the present compounds and other agents  
13 such as Minoxidil<sup>R</sup>, diseases associated with the immune system,  
14 including use of the present compounds as immunosuppressants and  
15 immunostimulants, modulation of organ transplant rejection and  
16 facilitation of wound healing, including modulation of chelosis.

17 This invention also relates to a pharmaceutical formulation  
18 comprising a compound of **Formula 1** in admixture with a  
19 pharmaceutically acceptable excipient.

20 In another aspect, this invention relates to processes for making a  
21 compound of **Formula 1** which processes comprise reacting a  
22 compound of **Formula 2**, or a suitable salt such as a sodium salt of a  
23 compound of **Formula 2** with a compound of **Formula 3** (where X<sub>1</sub> is  
24 halogen and Y, R<sub>2</sub>, A and B are defined as in connection with **Formula**  
25 **1**) in the presence of base and preferably in the presence of a catalyst,  
26 and also to the processes of oxidizing a sulfide compound of **Formula 1**  
27 (p = 0) to the corresponding sulfoxide or sulfone compound of  
28 **Formula 1** (p = 1 or p = 2).



#### Formula 2

#### Formula 3

Still further, the present invention relates to such reactions performed on the compounds of **Formula 1** which cause transformations of the B group while the reaction product still remains within the scope of **Formula 1**.

### General Embodiments

#### Definitions

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and cycloalkenyl groups having one or more sites of unsaturation. Similarly, the term alkynyl refers to and covers normal alkynyl, and branch chain alkynyl groups having one or more triple bonds.

Lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons in case of normal lower alkyl, and as

1 applicable 3 to 6 carbons for lower branch chained and cycloalkyl  
2 groups. Lower alkenyl is defined similarly having 2 to 6 carbons for  
3 normal lower alkenyl groups, and 3 to 6 carbons for branch chained  
4 and cyclo- lower alkenyl groups. Lower alkynyl is also defined similarly,  
5 having 2 to 6 carbons for normal lower alkynyl groups, and 4 to 6  
6 carbons for branch chained lower alkynyl groups.

7 The term "ester" as used here refers to and covers any compound  
8 falling within the definition of that term as classically used in organic  
9 chemistry. It includes organic and inorganic esters. Where B of  
10 Formula 1 is -COOH, this term covers the products derived from  
11 treatment of this function with alcohols or thioalcohols preferably with  
12 aliphatic alcohols having 1-6 carbons. Where the ester is derived from  
13 compounds where B is -CH<sub>2</sub>OH, this term covers compounds derived  
14 from organic acids capable of forming esters including phosphorous  
15 based and sulfur based acids, or compounds of the formula  
16 -CH<sub>2</sub>OCOR<sub>11</sub> where R<sub>11</sub> is any substituted or unsubstituted aliphatic,  
17 aromatic, heteroaromatic or aliphatic aromatic group, preferably with  
18 1-6 carbons in the aliphatic portions.

19 Unless stated otherwise in this application, preferred esters are  
20 derived from the saturated aliphatic alcohols or acids of ten or fewer  
21 carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and  
22 acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters  
23 are those derived from lower alkyl acids and alcohols. Also preferred  
24 are the phenyl or lower alkyl phenyl esters.

25 Amides has the meaning classically accorded that term in organic  
26 chemistry. In this instance it includes the unsubstituted amides and all  
27 aliphatic and aromatic mono- and di- substituted amides. Unless stated  
28 otherwise in this application, preferred amides are the mono- and

1 di-substituted amides derived from the saturated aliphatic radicals of  
2 ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic  
3 radicals of 5 to 10 carbon atoms. Particularly preferred amides are  
4 those derived from substituted and unsubstituted lower alkyl amines.  
5 Also preferred are mono- and disubstituted amides derived from the  
6 substituted and unsubstituted phenyl or lower alkylphenyl amines.  
7 Unsubstituted amides are also preferred.

8 Acetals and ketals include the radicals of the formula-CK where  
9 K is  $(-OR)_2$ . Here, R is lower alkyl. Also, K may be  $-OR_1O-$  where R,  
10 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

11 A pharmaceutically acceptable salt may be prepared for any  
12 compound in this invention having a functionality capable of forming  
13 such-salt, for example an acid functionality. A pharmaceutically  
14 acceptable salt is any salt which retains the activity of the parent  
15 compound and does not impart any deleterious or untoward effect on  
16 the subject to which it is administered and in the context in which it is  
17 administered. Pharmaceutically acceptable salts may be derived from  
18 organic or inorganic bases. The salt may be a mono or polyvalent ion.  
19 Of particular interest are the inorganic ions, sodium, potassium,  
20 calcium, and magnesium. Organic salts may be made with amines,  
21 particularly ammonium salts such as mono-, di- and trialkyl amines or  
22 ethanol amines. Salts may also be formed with caffeine, tromethamine  
23 and similar molecules. Where there is a nitrogen sufficiently basic as to  
24 be capable of forming acid addition salts, such may be formed with any  
25 inorganic or organic acids or alkylating agent such as methyl iodide.  
26 Preferred salts are those formed with inorganic acids such as  
27 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of  
28 simple organic acids such as mono-, di- or tri- acid may also be used.

1           Some of the compounds of the present invention may have trans  
2   and cis (E and Z) isomers. In addition, the compounds of the present  
3   invention may contain one or more chiral centers and therefore may  
4   exist in enantiomeric and diastereomeric forms. The scope of the  
5   present invention is intended to cover all such isomers per se, as well as  
6   mixtures of cis and trans isomers, mixtures of diastereomers and  
7   racemic mixtures of enantiomers (optical isomers) as well.

8           With reference to the symbol Y in Formula 1, the preferred  
9   compounds of the invention are those where Y is phenyl, pyridyl,  
10   2-thiazolyl, thienyl, or furyl, even more preferably, phenyl, pyridyl and  
11   2-thiazolyl. As far as substitutions on the Y (phenyl) and Y (pyridyl)  
12   groups are concerned, compounds are preferred where the phenyl  
13   group is 1,4 (para) substituted by the S=(O)<sub>p</sub> and A-B groups, and  
14   where the pyridine ring is 2,5 substituted by the S=(O)<sub>p</sub> and A-B  
15   groups. (Substitution in the 2,5 positions in the "pyridine"  
16   nomenclature corresponds to substitution in the 6-position in the  
17   "nicotinic acid" nomenclature.) When the Y group is thiazole it is  
18   preferably substituted in the 2 position by the S=(O)<sub>p</sub> group and in the  
19   5 position by the A-B group. In the preferred compounds of the  
20   invention there is no optional R<sub>2</sub> substituent on the Y group.

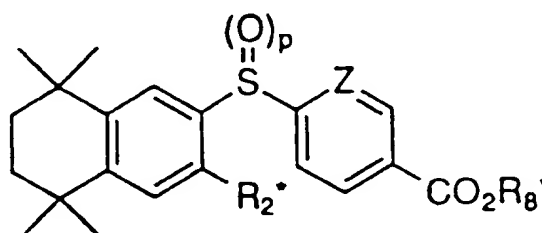
21           With reference to the symbol X in Formula 1, compounds are  
22   preferred in accordance with the invention where X is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> and n is  
23   1, and also where X is O or S (chroman and thiochroman derivatives).  
24   Even more preferred are compounds where X is [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> and n is 1  
25   (tetrahydronaphthalene derivatives). The presently preferred  
26   compounds of the invention are sulfides, and therefore p of Formula 1  
27   is preferably zero.

28           The R<sub>1</sub> groups are preferably H or CH<sub>3</sub>, and the preferred R<sub>2</sub>

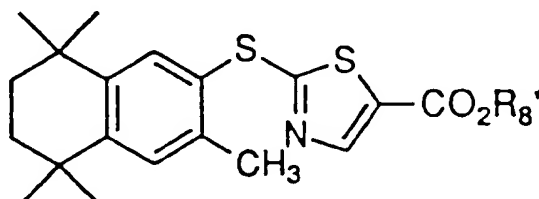
1 group on the aromatic portion of the condensed ring moiety is H, lower  
2 alkyl, F or CF<sub>3</sub>, even more preferably H or CH<sub>3</sub>. The R<sub>3</sub> group is  
3 preferably hydrogen; in other words the non-aromatic portion of the  
4 condensed ring moiety is preferably substituted only by the R<sub>1</sub> groups.

5 The A-B group of the preferred compounds is (CH<sub>2</sub>)<sub>n</sub>-COOH or  
6 (CH<sub>2</sub>)<sub>n</sub>-COOR<sub>8</sub>, where n and R<sub>8</sub> are defined as above. Even more  
7 preferably n is zero and R<sub>8</sub> is lower alkyl, or n is zero and B is COOH  
8 or a pharmaceutically acceptable salt thereof.

9 The presently most preferred compounds of the invention are  
10 shown in Table 1 with reference to Formula 4 and Formula 5.



18 Formula 4



28 Formula 5

TABLE 1

1	2	3	4	5	6	7
	Compound	Formula	p	Z	R <sub>1</sub> <sup>•</sup>	R <sub>2</sub> <sup>•</sup>
	#					
4	1	4	0	CH	H	Et
5	2	4	0	CH	H	H
6	3	4	1	CH	H	Et
7	4	4	2	CH	H	Et
8	5	4	2	CH	H	H
9	6	4	0	CH	CH <sub>3</sub>	Et
10	7	4	0	CH	CH <sub>3</sub>	H
11	8	4	1	CH	CH <sub>3</sub>	Et
12	9	4	1	CH	CH <sub>3</sub>	H
13	10	4	2	CH	CH <sub>3</sub>	Et
14	11	4	2	CH	CH <sub>3</sub>	H
15	12	4	0	N	CH <sub>3</sub>	Et
16	13	4	0	N	CH <sub>3</sub>	H
17	14	5	0	-	-	Et
18	15	5	0	-	-	H

19

20

Modes of Administration

21

22 The compounds of this invention may be administered  
 23 systemically or topically, depending on such considerations as the  
 24 condition to be treated, need for site-specific treatment, quantity of  
 25 drug to be administered, and numerous other considerations.

26

27 In the treatment of dermatoses, it will generally be preferred to  
 28 administer the drug topically, though in certain cases such as treatment  
 of severe cystic acne or psoriasis, oral administration may also be used.  
 Any common topical formulation such as a solution, suspension, gel,

1 ointment, or salve and the like may be used. Preparation of such  
2 topical formulations are well described in the art of pharmaceutical  
3 formulations as exemplified, for example, Remington's Pharmaceutical  
4 Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania.  
5 For topical application, these compounds could also be administered as  
6 a powder or spray, particularly in aerosol form. If the drug is to be  
7 administered systemically, it may be confected as a powder, pill, tablet  
8 or the like or as a syrup or elixir suitable for oral administration. For  
9 intravenous or intraperitoneal administration, the compound will be  
10 prepared as a solution or suspension capable of being administered by  
11 injection. In certain cases, it may be useful to formulate these  
12 compounds by injection. In certain cases, it may be useful to formulate  
13 these compounds in suppository form or as extended release  
14 formulation for deposit under the skin or intramuscular injection.

15 Other medicaments can be added to such topical formulation for  
16 such secondary purposes as treating skin dryness; providing protection  
17 against light; other medications for treating dermatoses; medicaments  
18 for preventing infection, reducing irritation, inflammation and the like.

19 Treatment of dermatoses or any other indications known or  
20 discovered to be susceptible to treatment by retinoic acid-like  
21 compounds will be effected by administration of the therapeutically  
22 effective dose of one or more compounds of the instant invention. A  
23 therapeutic concentration will be that concentration which effects  
24 reduction of the particular condition, or retards its expansion. In certain  
25 instances, the compound potentially may be used in prophylactic  
26 manner to prevent onset of a particular condition.

27 A useful therapeutic or prophylactic concentration will vary from  
28 condition to condition and in certain instances may vary with the



1 severity of the condition being treated and the patient's susceptibility to  
2 treatment. Accordingly, no single concentration will be uniformly  
3 useful, but will require modification depending on the particularities of  
4 the disease being treated. Such concentrations can be arrived at  
5 through routine experimentation. However, it is anticipated that in the  
6 treatment of, for example, acne, or similar dermatoses, that a  
7 formulation containing between 0.01 and 1.0 milligrams per milliliter of  
8 formulation will constitute a therapeutically effective concentration for  
9 total application. If administered systemically, an amount between 0.01  
10 and 5 mg per kg per day of body weight would be expected to effect a  
11 therapeutic result in the treatment of many disease for which these  
12 compounds are useful.

13 Assay of Retinoid-like Biological Activity

14 The retinoid-like activity of the compounds of the invention can  
15 be confirmed in assays wherein ability of the compound to modulate  
16 processes mediated by retinoid receptors, and ability of the compounds  
17 to bind to retinoid receptors is measured. As it is noted in the  
18 introductory section of this application for patent two main types of  
19 retinoic acid receptors (RAR and RXR) exist in mammals (and other  
20 organisms). Within each type there are sub-types (RAR<sub>α</sub>, RAR<sub>β</sub>,  
21 RAR<sub>γ</sub>, RXR<sub>α</sub>, RXR<sub>β</sub> and RXR<sub>γ</sub>) the distribution of which is not  
22 uniform in the various tissues and organs of mammalian organisms.  
23 Moreover, specific or selective agonist-like activity on RXR receptors,  
24 in preference over RAR receptors tends to result in certain beneficial  
25 retinoid-like properties while avoiding certain undesirable side effects.  
26 Similarly, selective agonist like activity of only one or two retinoid  
27 receptor subtypes within one retinoid receptor family can also give rise  
28 to beneficial pharmacological properties because of the varying

1 distribution of the sub-types in the several mammalian tissues or organs.  
2 For the above-summarized reasons, agonist-like activity in any or all of  
3 the retinoid receptors, as well as specific or selective activity in the  
4 RXR receptor family, or selective or specific activity in any one of the  
5 receptor subtypes, are all considered desirable pharmacological  
6 properties.

7 In light of the foregoing the prior art has developed assay  
8 procedures for testing the agonist like activity of compounds in the  
9 RAR $\alpha$ , RAR $\beta$ , RAR $\gamma$ , RXR $\alpha$ , RXR $\beta$  and RXR $\gamma$  receptor subtypes. For  
10 example, a **chimeric receptor transactivation assay** which tests for  
11 agonist-like activity in the RAR $\alpha$ , RAR $\beta$ , RAR $\gamma$ , RXR $\alpha$  receptor  
12 subtypes, and which is based on work published by Feigner P. L. and  
13 Holm M. (1989) Focus, 11 2 is described in detail in U.S. Patent No.  
14 5,455,265. The specification of United States Patent No. 5,455,265 is  
15 expressly incorporated herein by reference.

16 A **holoreceptor transactivation assay** and a **ligand binding assay**  
17 which measure the ability of the compounds of the invention to bind to  
18 the several retinoid receptor subtypes, respectively, are described in  
19 published PCT Application No. WO WO93/11755 (particularly on pages  
20 30 - 33 and 37 - 41) published on June 24, 1993, the specification of  
21 which is also incorporated herein by reference. A description of the  
22 **holoreceptor transactivation assay** is also provided below.

### 23 **HOLORECEPTOR TRANSACTIVATION ASSAY**

24 CV1 cells (5,000 cells/well) were transfected with an RAR  
25 reporter plasmid MTV-TREp-LUC (50 ng) along with one of the RAR  
26 expression vectors (10 ng) in an automated 96-well format by the  
27 calcium phosphate procedure of Heyman et al. Cell 68, 397 - 406. (8).  
28 For RXR $\alpha$  and RXR $\gamma$  transactivation assays, an RXR-responsive

1 reporter plasmid CRBP<sub>II</sub>-tk-LUC (50 ng) along with the appropriate  
2 RXR expression vectors (10 ng) was used substantially as described by  
3 Heyman et al. above, and Allegretto et al. J. Biol. Chem. 268, 26625 -  
4 26633. For RXR<sub>β</sub> transactivation assays, an RXR-responsive reporter  
5 plasmid CPRE-tk-LUC (50 mg) along with RXR<sub>β</sub> expression vector (10  
6 mg) was used as described in above. These reporters contain DRI  
7 elements from human CRBP<sub>II</sub> and certain DRI elements from  
8 promoter, respectively. (see Mangelsdorf et al. The Retinoids: Biology,  
9 Chemistry and Medicine, pp 319 - 349, Raven Press Ltd., New York  
10 and Heyman et al., cited above) (1, 8). A β-galactosidase (50 ng)  
11 expression vector was used as an internal control in the transfections to  
12 normalize for variations in transfection efficiency. The cells were  
13 transfected in triplicate for 6 hours, followed by incubation with  
14 retinoids for 36 hours, and the extracts were assayed for luciferase and  
15 β-galactosidase activities. The detailed experimental procedure for  
16 holoreceptor transactivations has been described in Heyman et al.  
17 above, and Allegretto et al. cited above. The results obtained in this  
18 assay in connection with exemplary compounds in accordance with the  
19 present invention are expressed in EC<sub>50</sub> numbers, as they are also in the  
20 chimeric receptor transactivation assay. The Heyman et al. Cell 68,  
21 397 - 406, Allegretto et al. J. Biol. Chem. 268, 26625 - 26633, and  
22 Mangelsdorf et al. The Retinoids: Biology, Chemistry and Medicine, pp  
23 319 - 349, Raven Press Ltd., New York, are expressly incorporated  
24 herein by reference. The results of ligand binding assay are expressed  
25 in K<sub>d</sub> numbers. (See Cheng et al. Biochemical Pharmacology Vol. 22  
26 pp 3099-3108, expressly incorporated herein by reference.)

27 Table 2 below shows the results of the holoreceptor  
28 transactivation assay and Table 3 discloses the efficacy (in percentage)

1 in this assay of the test compound relative to all *trans* retinoic acid, for  
 2 certain exemplary compounds of the invention. Table 4 shows the  
 3 results of the ligand binding assay for certain exemplary compounds of  
 4 the invention.

5

6

TABLE 2

7

## Holoreceptor Transactivation Assay

8

Compound #

EC<sub>50</sub> (nanomolar)

9

RAR $\alpha$  RAR $\beta$  RAR $\gamma$  RXR $\alpha$  RXR $\beta$  RXR $\gamma$ 

10	2	0.00	570	340	770	1600	1600
11	5	0.00	0.00	0.00	3000	0.00	2600
12	7	0.00	0.00	0.00	280	320	230
13	9	0.00	0.00	0.00	0.00	3000	1600
14	11	0.00	0.00	0.00	2800	2600	2600
15	13	0.00	0.00	0.00	54	57	42
16	15	0.00	0.00	0.00	2300	1300	1900

17 O.O in Table 2 indicates that the compound is less than 20 % as active  
 18 (efficacious) in this assay than all trans retinoic acid.

19

20

TABLE 3

21

## Transactivation Assay Efficacy (% of RA activity)

22

Compound #

23

RAR $\alpha$  RAR $\beta$  RAR $\gamma$  RXR $\alpha$  RXR $\beta$  RXR $\gamma$ 

24	2	3	66	37	51	80	75
25	5	10	4	0	32	11	26
26	7	3	4	11	81	114	67
27	9	5	4	3	17	29	28
28	11	2	6	0	55	52	45
29	13	1	4	0	91	100	85
30	15	1	0	7	85	117	70

TABLE 4

## Ligand Binding Assay

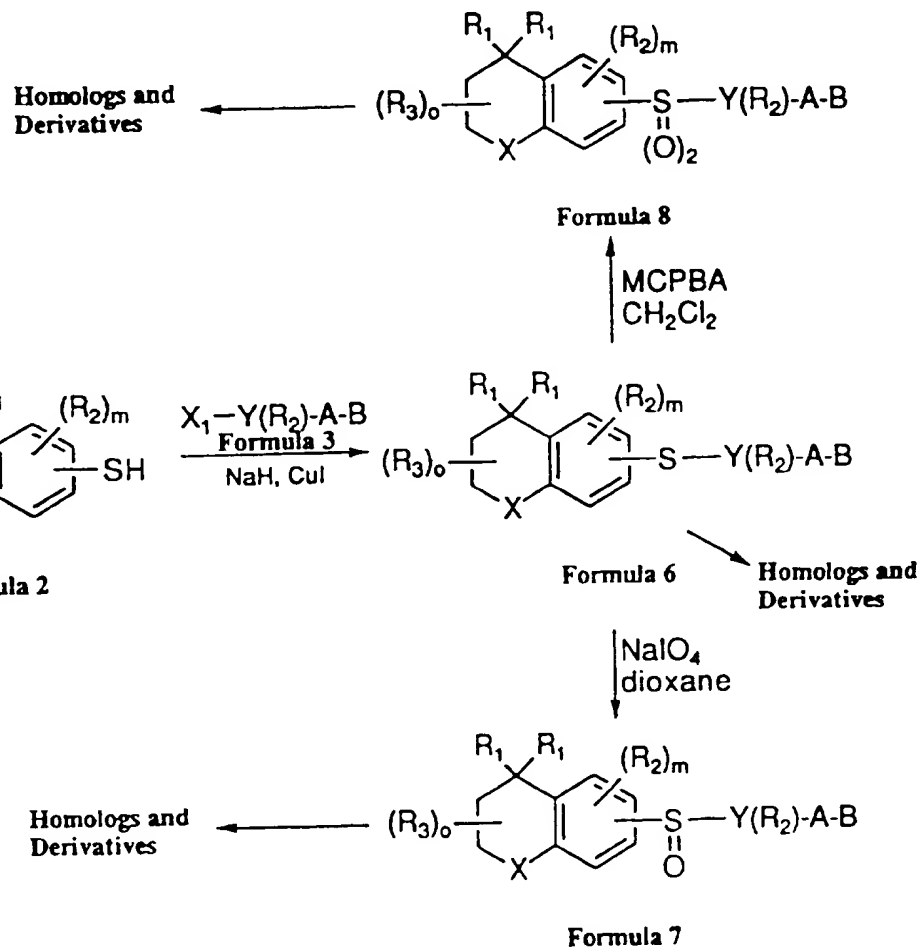
3	Compound #	K <sub>d</sub> (nanomolar)					
4		RAR $\alpha$	RAR $\beta$	RAR $\gamma$	RXR $\alpha$	RXR $\beta$	RXR $\gamma$
5	2	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
6	5	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
7	7	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	296	302	304
8	9	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
9	11	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>
10	13	>10 <sup>4</sup>	>10 <sup>4</sup>	>10 <sup>4</sup>	32	57	73
11	15	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>	>10 <sup>3</sup>

12 As it can be seen from the test results summarized in Tables 2, 3  
 13 and 4, the therein indicated exemplary compounds of the invention are  
 14 substantially inactive as RAR agonists but are active agonists of all or  
 15 some of the RXR receptor subtypes.

## SPECIFIC EMBODIMENTS

17 The compounds of this invention can be made by the synthetic  
 18 chemical pathways illustrated here. The synthetic chemist will readily  
 19 appreciate that the conditions set out here are specific embodiments  
 20 which can be generalized to any and all of the compounds represented  
 21 by Formula 1.

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Reaction Scheme 1

1           In accordance with **Reaction Scheme 1**, a condensed cyclic thiol  
2 compound of **Formula 2** which is appropriately substituted with the  $R_1$ ,  
3  $R_2$  and  $R_3$  groups (as these are defined in connection with **Formula 1**)  
4 serves as the starting material. The thiol compound of **Formula 2** is  
5 reacted in the presence of strong base, such as sodium hydride, in a  
6 polar aprotic solvent, such as dimethylformamide or  
7 hexamethylphosphoramide, and a catalyst, such as copper iodide (CuI),  
8 with a reagent of **Formula 3** where  $X_1$  is halogen and Y,  $R_2$ , A and B  
9 are defined as in connection with **Formula 1**. The reagent of **Formula**  
10 **3** is, generally speaking, available in accordance with the chemical  
11 scientific or patent literature. In the presently preferred compounds of  
12 the invention the A group is  $(CH_2)_q$  and B is COOH or an ester or  
13 amide thereof ( $COOR_8$  or  $CONR_9R_{10}$ ) and even more preferably q is  
14 zero. The presently preferred reagents in accordance with **Formula 3**  
15 used for preparation of compounds of the invention have the structure  
16  $X_1-Y(R_2)-COOR_8$ , and preferred examples are ethyl 4-iodobenzoate  
17 (available commercially from Lancaster Chemical Co.),  
18 ethyl-2-iodonicotinate and ethyl 2-iodo-5-thiazolecarboxylate. The  
19 preparations of ethyl-2-iodonicotinate and of ethyl  
20 2-iodo-5-thiazolecarboxylate are described below in the experimental  
21 section.

22           The thiol reagent of **Formula 2** is, generally speaking, also  
23 available in accordance with the chemical scientific and patent  
24 literature. In one group of preferred compounds of the invention the X  
25 group is  $[C(R_1)]_n$  where n is 1 (tetrahydronaphthalene derivatives) and  
26 an example of the starting material for several preferred  
27 tetrahydronaphthalene derivatives of the invention is

1 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthiol. The latter  
2 compound is available as a result of chlorosulfonylation followed by  
3 lithium aluminum hydride reduction of  
4 5,6,7,8-tetrahydro-5,5,8,8-tetramethylhaphthalene in accordance with the  
5 procedure of Janssen et al.(BASF A.-G.): Diphenylheteroalkylderivate,  
6 ihre Herstellung und daraus hergestellte Arzneimittel und Kosmetika,  
7 European Patent Application EP 0 386 452 A1 (September 12, 1990),  
8 incorporated herein by reference. The above-mentioned  
9 chlorosulfonylation reaction followed by lithium aluminum hydride  
10 reduction to provide a thiol compound in the scope of **Formula 2** is,  
11 generally speaking, applicable for preparing the starting materials (i. e.  
12 compounds of **Formula 2**) for the synthesis of the compounds of the  
13 present invention.

14 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalene thiol is  
15 described in Chemical Abstracts 111:97241 and in French patent FR  
16 2614618 A1, 11-04-1988, incorporated herein by reference.

17 Chroman-6-thiol is described in Chemical Abstracts 101:8709 and in  
18 German patent DE 3314467 A1, 01-19-1984, incorporated herein by  
19 reference. 2,2-Dimethylchroman-6-thiol is described in Chemical  
20 Abstracts 117:48593 and in Japanese patent JP 03232882 A2  
21 10-16-1991, incorporated herein by reference.

22 In addition to the availability of the thiol compounds of **Formula**  
23 **2** from the foregoing and other scientific publications and patent  
24 description (through the above-mentioned chlorosulfonation reaction  
25 followed by reduction with  $\text{LiAlH}_4$ ) the thiol compounds can also be  
26 prepared from bromo substituted tetrahydronaphthalene, chroman,  
27 thiochroman and tetrahydroquinoline compounds which are known or  
28 available in the art. For example, United States Patent Nos. 5,278,318,



1 5,348,972, 5,407,937, and 5,407,937 describe 2-alkyl and/or 4-alkyl  
2 substituted thiochromans also substituted with a bromo group in the 6  
3 position. United States Patent No. 5,346,585 describes 2-alkyl and/or  
4 4-alkyl substituted thiochromans substituted with a bromo group in the  
5 7 position. United States Patent Nos. 5,324,744, 5,348,975 and  
6 5,346,585 describe 2-alkyl and/or 4-alkyl substituted chromans  
7 substituted with a bromo group in the 7 position. United States Patent  
8 No. 5,348,972 describes 4-alkyl substituted tetrahydroquinoline  
9 compounds substituted with a bromo group in the 6 position. The  
10 specifications of United States Patent Nos. 5,278,318, 5,324,744,  
11 5,346,585, 5,348,972, 5,348,975, and 5,407,937 are expressly incorporated  
12 herein by reference. These and analogous bromo compounds can be  
13 reacted with 2 equivalents of *t*-butyl lithium in an inert ether-type  
14 solvent, and the resulting anion formed after lithium halogen exchange  
15 is quenched with sulfur to provide the thiol compounds of **Formula 2**.

16 Referring back again to **Reaction Scheme 1** the reaction between  
17 the thiol compounds of **Formula 2** and the aromatic or heteroaromatic  
18 halogenated compounds of **Formula 3** gives rise to the disubstituted  
19 sulfide compounds of **Formula 6**. The disubstituted sulfide compounds  
20 of **Formula 6** are within the scope of the present invention and  
21 represent a class of preferred compounds of the invention, where with  
22 reference to **Formula 1**, *p* is zero. The compounds of **Formula 6** are  
23 oxidized to provide the sulfoxide compounds of **Formula 7** which are  
24 also within the scope of the invention and where, with reference to  
25 **Formula 1**, *p* is 1. The oxidation to the sulfoxide stage is conducted  
26 with a suitable oxidizing agent, such as sodium periodate ( $\text{NaIO}_4$ ) in an  
27 ether like solvent, such as dioxane. The disubstituted sulfide  
28 compounds of **Formula 6** are also oxidized in accordance with **Reaction**

1    Scheme 1 to the sulfone compounds of **Formula 8**, which are also  
2    within the scope of the present invention. In these compounds, with  
3    reference to **Formula 1**, **p** is 2. Oxidation to the sulfone stage is carried  
4    out by reaction with a strong oxidizing agent, such as  
5    m-chloroperoxybenzoic acid in an aprotic solvent, preferably methylene  
6    chloride. In the situations where the **X** group of **Formula 1** is sulfur  
7    (thiochroman derivatives), the above-described oxidation reactions may  
8    also oxidize the ring sulfur to the sulfoxide and/or sulfone stage,  
9    respectively.

10        In addition to the above described oxidation reactions the  
11    compounds of **Formulas 6, 7 and 8** can be subjected to such further  
12    transformations, primarily affecting the **A-B** group, which are per se  
13    well known in the art, and which result in still further compounds  
14    within the scope of **Formula 1**. Reactions frequently carried out which  
15    affect the **B** group typically are saponification of an ester group,  
16    esterification of a carboxylic acid, formation of an amide or  
17    homologation of an acid or ester. These reactions are indicated in  
18    **Reaction Scheme 1** by conversion to "homologs and derivatives".  
19    Regarding these reactions and also regarding the synthesis of  
20    halogenated compounds of **Formula 3** suitable for the coupling  
21    reactions described in **Reaction Scheme 1** (where such compound is not  
22    available commercially or from a known literature procedure) the  
23    following general synthetic methodology is noted.

24        Carboxylic acids are typically esterified by refluxing the acid in a  
25    solution of the appropriate alcohol in the presence of an acid catalyst  
26    such as hydrogen chloride or thionyl chloride. Alternatively, the  
27    carboxylic acid can be condensed with the appropriate alcohol in the  
28    presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The

1 ester is recovered and purified by conventional means. Acetals and  
2 ketals are readily made by the method described in March, "Advanced  
3 Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810).  
4 Alcohols, aldehydes and ketones all may be protected by forming  
5 respectively, ethers and esters, acetals or ketals by known methods such  
6 as those described in McOmie, Plenum Publishing Press, 1973 and  
7 Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

8 A means for making compounds where A is  $(CH_2)_q$  (q is 1 - 5) is  
9 to subject the compounds of **Formula 1**, where B is an acid or other  
10 function, to homologation, using the well known Arndt-Eistert method  
11 of homologation, or other known homologation procedures. Similar  
12 homologations (and several of the other herein mentioned synthetic  
13 transformations) can be transformed on the reagent  $X_1-Y(R_2)-A-B$ .  
14 Compounds of the invention, where A is an alkenyl group having one or  
15 more double bonds can be made, for example, by having the requisite  
16 number of double bonds incorporated into the reagent  $X_1-Y(R_2)-A-B$ .  
17 Generally speaking, such compounds where A is an unsaturated carbon  
18 chain can be obtained by synthetic schemes well known to the  
19 practicing organic chemist; for example by Wittig and like reactions, or  
20 by introduction of a double bond by elimination of halogen from an  
21 alpha-halo-carboxylic acid, ester or like carboxaldehyde. Compounds of  
22 the invention where the A group has a triple (acetylenic) bond can be  
23 made by using the corresponding aryl or heteroaryl aldehyde  
24 intermediate. Such intermediate can be obtained by reactions well  
25 known in the art, for example, by reaction of a corresponding methyl  
26 ketone with strong base, such as lithium diisopropylamide.

27 The acids and salts derived from compounds of **Formula 1** are  
28 readily obtainable from the corresponding esters. Basic saponification

1 with an alkali metal base will provide the acid. For example, an ester  
2 of **Formula 1** may be dissolved in a polar solvent such as an alkanol,  
3 preferably under an inert atmosphere at room temperature, with about  
4 a three molar excess of base, for example, potassium or lithium  
5 hydroxide. The solution is stirred for an extended period of time,  
6 between 15 and 20 hours, cooled, acidified and the hydrolysate  
7 recovered by conventional means.

8 The amide may be formed by any appropriate amidation means  
9 known in the art from the corresponding esters or carboxylic acids.  
10 One way to prepare such compounds is to convert an acid to an acid  
11 chloride and then treat that compound with ammonium hydroxide or an  
12 appropriate amine.

13 Alcohols are made by converting the corresponding acids to the  
14 acid chloride with thionyl chloride or other means (J. March,  
15 "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book  
16 Company), then reducing the acid chloride with sodium borohydride  
17 (March, Ibid, pg. 1124), which gives the corresponding alcohols.  
18 Alternatively, esters may be reduced with lithium aluminum hydride at  
19 reduced temperatures. Alkylating these alcohols with appropriate alky  
20 halides under Williamson reaction conditions (March, Ibid, pg. 357)  
21 gives the corresponding ethers. These alcohols can be converted to  
22 esters by reacting them with appropriate acids in the presence of acid  
23 catalysts or dicyclohexylcarbodiimide and dimethylaminopyridine.

24 Aldehydes can be prepared from the corresponding primary  
25 alcohols using mild oxidizing agents such as pyridinium dichromate in  
26 methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or  
27 dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K.,  
28 Swern, D., Tetrahedron, 1978, 34, 1651).

1 Ketones can be prepared from an appropriate aldehyde by  
2 treating the aldehyde with an alkyl Grignard reagent or similar reagent  
3 followed by oxidation.

4 Acetals or ketals can be prepared from the corresponding  
5 aldehyde or ketone by the method described in March, Ibid, p 810.

6 Compounds of **Formula 1** where **B** is H can be prepared from  
7 the corresponding halogenated aromatic compounds, preferably where  
8 the halogen is I.

### 9 Specific Examples

#### 10 6-Iodonicotinic acid

11 To 27.97 g (186.6 mmol) of sodium iodide cooled to -78°C was  
12 added 121.77 g (71.6 ml, 952.0 mmol) of hydroiodic acid (57 wt %).  
13 The reaction mixture was allowed to warm slightly with stirring for 5  
14 minutes, and then 30.00 g (190.4 mmol) of 6-chloronicotinic acid was  
15 added. The resulting mixture was allowed to warm to room  
16 temperature with stirring and then heated at 120-125°C in an oil bath  
17 for 42 hours. A dark brown layer formed above the yellow solid  
18 material. The reaction mixture was allowed to cool to room  
19 temperature and then poured into acetone (chilled to 0°C). The  
20 resultant yellow solid was collected by filtration, washed with 200 ml of  
21 1N NaHSO<sub>3</sub> solution, and dried in high vacuum (3 mm Hg) to give the  
22 title compound as a pale yellow solid.  
23 PMR (DMSO-d<sub>6</sub>): δ 7.90 (1H, dd, J = 8.1, 2 Hz), 7.99 (1H, d, J = 8.1  
24 Hz), 8.80 (1H, d, J = 2.Hz).

#### 25 Ethyl 6-iodonicotinate

26 To a suspension of 23.38 g (94.2 mmol) of 6-iodonicotinic acid in  
27 100 ml of dichloromethane was added a solution of 19.86 g (103.6  
28 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

1 in 250 ml of dichloromethane. To this suspension was added 12.40 g  
2 (15.8 ml, 269.3 mmol) of ethanol (95%) and 1.15 g (9.4 mmol) of  
3 4-dimethylaminopyridine. The resulting solution mixture was then  
4 heated at 50°C in an oil bath for 24.5 hours, concentrated in vacuo,  
5 partitioned between 200 ml of water and 250 ml of ethyl ether, and the  
6 layers were separated. The aqueous phase was washed with 2 x 150  
7 ml-portions of ethyl ether. All organic phases were combined, washed  
8 once with 75 ml of brine solution, dried over  $\text{MgSO}_4$ , filtered and  
9 concentrated in vacuo to a yellow solid. Purification by flash  
10 chromatography (silica, 10% ethyl acetate in hexane) yielded the title  
11 compound as a white solid.

12 PMR ( $\text{CDCl}_3$ ):  $\delta$  1.41 (3H, t,  $J = 7.1$  Hz), 4.41 (2H, q,  $J = 7.1$  Hz),  
13 7.85 (1H, d,  $J = 8.2$  Hz), 7.91 (1H, dd,  $J = 8.2, 2.1$  Hz), 8.94 (1H, d,  $J$   
14  $= 2.1$  Hz).

15 Ethyl 2-iodo-5-thiazolecarboxylate

16 To a solution of 4.96 g (31.5 mmol) of 2-trimethylsilylthiazole in  
17 100 ml of ether stirring at -78 °C under argon, was dropwise added  
18 n-BuLi (23.0 mL, 36.8 mmol, 1.6 M in hexanes) and the resulting  
19 mixture stirred at -78 °C for 30 min. Ethyl chloroformate (7.60 mL,  
20 10.6 g, 98 mmol) was added and the reaction stirred at -78 °C for 30  
21 min and at room temperature for 30 min. The solution was then  
22 recooled to -78 °C where a solution of 10.75 g (42.5 mmol) of  $\text{I}_2$  in 50  
23 mL of tetrahydrofuran was cannulated into the cool solution. The  
24 reaction was warmed slowly to room temperature and stirred for 15 h.  
25 The reaction was then cooled to -78 °C, quenched with water and  
26 sodium thiosulfate, and extracted with diethyl ether (3x). The organic  
27 layers were combined, washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and  
28 the solvents removed in-vacuo. The crude product was purified by

1 flash chromatography on silica gel (85:15/hexane:ethyl acetate) to give  
2 the title compound as an oil (0.89 g, 10%):  
3 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.38 (t, 3H, J = 7.1 Hz), 4.36 (q, 2H, J =  
4 7.1 Hz), 8.11 (s, 1H).

5 Ethyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate  
6 (Compound 1)

7 Sodium hydride (0.807 g, 60% dispersion in oil, 21 mmol) was  
8 rinsed 3x with hexane and dried under vacuum. The vacuum was  
9 broken with dry argon and to this was added 10.0 mL of  
10 dimethylformamide and the mixture cooled to 0 °C.  
11 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthylthiol available in  
12 accordance with Janssen et al. European Patent Application EP 0 386  
13 452 A1, September 12, 1990, (702 mg, 3.2 mmol) was then added and  
14 the resulting mixture stirred at 0-10 °C for 1.25 h. Copper (I) iodide  
15 (0.592 g, 3.1 mmol) was added, the mixture stirred at 0 °C for 45 min  
16 and a solution of ethyl 4-iodobenzoate (0.839 g, 3.04 mmol) in 2.0 ml of  
17 dimethylformamide was added. The mixture was heated to 75 °C for 48  
18 h, the bath removed, and stirred at room temperature for 48 h. The  
19 reaction was then poured onto ice and extracted with ether (4x), the  
20 organic layers were combined, washed with brine, dried (MgSO<sub>4</sub>),  
21 filtered, and the solvents removed in-vacuo to give an orange solid.  
22 The crude product was purified by flash chromatography on silica gel  
23 (98:2/hexane:ethyl acetate) to give the title compound as a clear oil  
24 (0.32 g, 27%):  
25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26 (s, 6H), 1.30 (s, 6H), 1.37 (t, 3H, J =  
26 7.1 Hz), 1.70 (s, 4H), 4.34 (q, 2H, J = 7.1 Hz), 7.17 (d, 2H J = 8.5 Hz),  
27 7.22 (dd, 1H, J = 2.0, 8.2 Hz), 7.32 (d, 1H, J = 8.2 Hz), 7.44 (d, 1H, J  
28 = 2.0 Hz), 7.89 (d, 2H J = 8.5 Hz).

1 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoic acid

2 (Compound 2)

3 To a solution of 70 mg (0.19 mmol) of ethyl  
4 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoate  
5 (Compound 1) in 4.0 mL of tetrahydrofuran was added 1.0 mL of  
6 LiOH (1.9 N aqueous solution) and 1.5 mL of MeOH. The solution  
7 was heated at 55 °C for 3 h, cooled to room temperature and  
8 concentrated in vacuo. The residue was diluted with water and  
9 extracted with hexane. The aqueous layer was acidified to pH=1 using  
10 10% HCl and extracted twice with diethyl ether. The combined organic  
11 layers were washed with brine, dried (MgSO<sub>4</sub>), filtered and the solvents  
12 removed in vacuo. Purification of crude product by flash  
13 chromatography on silica gel (7:3/hexane:ethyl acetate) gave the title  
14 compound as a white solid (40 mg, 62%):  
15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.27 (s, 6H), 1.31 (s, 6H), 1.71 (s, 4H),  
16 7.18 (d, 2H J = 8.6 Hz), 7.25 (dd, 1H, J = 2.0, 8.2 Hz), 7.34 (d, 1H, J  
17 = 8.2 Hz), 7.47 (d, 1H, J = 2.0 Hz), 7.95 (d, 2H J = 8.6 Hz).

18 Ethyl

19 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfoxy)benzoate

20 (Compound 3)

21 To a solution of ethyl  
22 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate  
23 (Compound 1, 0.18 g, 0.31 mmol) in 4 ml of dioxane was dropwise  
24 added a solution of sodium periodate (0.181 g, 0.85 mmol) in 1.7 mL  
25 H<sub>2</sub>O and 4.0 mL of MeOH. The resulting mixture was stirred at 50 °C  
26 for 120 h. The reaction was then cooled to room temperature, brine  
27 was added and the mixture extracted using ether (2x). The combined  
28 organic layers were then dried (MgSO<sub>4</sub>), filtered and concentrated to



1 give a clear oil. Purification by flash chromatography  
2 (85:15/hexane:ethyl acetate) gave the title compound as a clear oil (57  
3 mg, 30%):  
4 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.24 (s, 6H), 1.26 (s, 3H), 1.28 (s, 3H),  
5 1.39 (t, 3H, J = 7.1 Hz), 1.67 (s, 4H), 4.38 (q, 2H, J = 7.1 Hz), 7.27  
6 (dd, 1H, J = 1.9, 8.3 Hz), 7.36 (d, 1H J = 8.3 Hz), 7.64 (d, 1H, J = 1.9  
7 Hz), 7.72 (d, 2H, J = 8.4 Hz), 8.14 (d, 2H J = 8.4 Hz).

8 Ethyl

9 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate  
10 (Compound 4)

11 To a solution of 230 mg (0.63 mmol) of ethyl  
12 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate  
13 (Compound 1) in 5.0 mL of methylene chloride was added  
14 m-chloroperoxybenzoic acid (200 mg, 0.60 mmol, 50-60%) and the  
15 resulting solution stirred at room temperature for 24 h. The reaction  
16 mixture was diluted with water and extracted with methylene chloride  
17 (2x). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and  
18 the solvents were removed in vacuo to give a white solid. The crude  
19 product was purified by flash chromatography on silica gel  
20 (96:4/hexane:ethyl acetate) to give the title compound as a white solid  
21 (0.11 g, 87%):

22 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (s, 6H), 1.29 (s, 6H), 1.39 (t, 3H, J =  
23 7.1 Hz), 1.68 (s, 4H), 4.39 (q, 2H, J = 7.1 Hz), 7.42 (d, 2H J = 8.4 Hz),  
24 7.61 (dd, 1H, J = 2.1, 8.4 Hz), 7.90 (d, 1H, J = 2.1 Hz), 8.00 (d, 2H J  
25 = 8.5 Hz), 8.15 (d, 2H J = 8.5 Hz).

26 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoic acid  
27 (Compound 5)

28 To a solution of 95 mg (0.23 mmol) of ethyl

1 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate  
2 (**Compound 4**) in 4.0 mL of tetrahydrofuran was added 1.0 mL of  
3 LiOH (2.6 N aqueous solution) and 1.4 mL of MeOH. The solution  
4 was heated at 55 °C for 2.5 h, cooled to room temperature and  
5 concentrated in vacuo. The residue was diluted with brine, acidified to  
6 pH = 1 using 10% HCl and extracted with ether (2x). The combined  
7 organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtered and the  
8 solvents were removed in vacuo to give the title compound as a white  
9 solid (80 mg, 91%):

10 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26 (s, 6H), 1.29 (s, 6H), 1.68 (s, 4H),  
11 7.17 (d, 2H J = 8.5 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.63 (dd, 1H, J =  
12 2.1, 8.4 Hz), 7.92 (d, 1H, J = 2.1 Hz), 8.04 (d, 2H J = 8.5 Hz), 8.22 (d,  
13 2H J = 8.5 Hz).

14 Ethyl

15 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate  
16 (**Compound 6**)

17 Sodium hydride (65 mg, 60 % dispersion in oil, 1.62 mmol) was  
18 rinsed 3x with hexane and dried under vacuum. The vacuum was  
19 broken with dry argon and 2.5 mL of hexamethylphosphoramide  
20 (HMPA) and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol  
21 (see Janssen et al. European Patent Application EP 0 386 452 A1)  
22 (0.38 g, 1.62 mmol) were added sequentially. After 30 min at 50 °C,  
23 copper (I) iodide (257 mg, 1.35 mmol) was added, which caused the  
24 solution to become deep green. The solution was stirred for 15 min  
25 and ethyl 4-iodobenzoate (373 mg, 1.35 mmol) was added. The  
26 solution was heated to 90 °C for 5 h, the bath removed, and stirring  
27 continued overnight at room temperature. Water was added and the  
28 products extracted with diethyl ether (3x). The combined ether layers

1 were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and the solvents  
2 removed in vacuo. The residue was purified by flash chromatography  
3 on silica gel (95:5/hexane:ethyl acetate) to give the title compound as a  
4 light yellow solid (260 mg, 50 %):

5  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.24 (s, 6H), 1.30 (s, 6H), 1.36 (t, 3H,  $J =$   
6 7.1 Hz), 1.69 (s, 4H), 2.28 (s, 3H), 4.33 (q, 2H,  $J = 7.1$  Hz), 7.05 (d,  
7 2H,  $J = 8.6$  Hz), 7.23 (s, 1H), 7.26 (s, 1H), 8.87 (d, 2H,  $J = 8.6$  Hz)  
8 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoic acid  
9 (Compound 7)

10 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-  
11 2-naphthylthio)benzoate (Compound 6, 170 mg, 0.44 mmol) was  
12 dissolved in ethyl alcohol (4 mL) and the solution treated with 2N  
13 aqueous KOH (2 mL). The solution was heated to 50 °C for 4 h and  
14 concentrated in vacuo. The residue was treated with diethyl ether,  
15 cooled to 0 °C, and acidified with 10% aqueous HCl. The product was  
16 extracted with diethyl ether, washed with water, brine, dried ( $\text{MgSO}_4$ ),  
17 filtered and the solvents were removed under reduced pressure to give  
18 the title compound as a yellow solid (158 mg, 100 %):

19  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.25 (s, 6H), 1.31 (s, 6H), 1.69 (s, 4H),  
20 2.29 (s, 3H), 7.05 (d, 2H,  $J = 8.5$  Hz), 7.25 (s, 1H), 7.26 (s, 1H), 7.92 (d,  
21 2H,  $J = 8.5$  Hz)

22 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)-  
23 benzoate (Compound 8)

24 To a solution of ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-  
25 pentamethyl-2-naphthylthio)benzoate (Compound 6, 0.12 g, 0.31 mmol)  
26 in 4 mL of dioxane was dropwise added 1.0 mL of 0.42M sodium  
27 periodate (0.42 mmol, 180 mg in 1.3 mL  $\text{H}_2\text{O}$  and 0.7 mL of MeOH).  
28 An additional 6.0 mL of methanol was added and the resulting mixture

1 was stirred at room temperature for 42 h. The reaction was then  
2 heated at 50 °C for 200 h. Additional sodium periodate (80 mg, 0.38  
3 mmol) and 2.0 mL of dioxane was added during this time. The reaction  
4 was then cooled to room temperature, brine was added and the mixture  
5 extracted using ether (2x). The organic layers were then dried  
6 ( $\text{MgSO}_4$ ), filtered and concentrated to give a clear oil. Purification by  
7 flash chromatography (85:15/hexane:ethyl acetate) gave the title  
8 compound as a clear oil (65 mg, 52%):  
9  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (s, 3H), 1.24 (s, 3H), 1.26 (s, 3H),  
10 1.30 (s, 3H), 1.39 (t, 3H,  $J = 7.1$  Hz), 1.67 (s, 4H), 2.31 (s, 3H), 4.38 (q,  
11 2H,  $J = 7.1$  Hz), 7.08 (s, 1H), 7.66 (d, 2H  $J = 8.4$  Hz), 7.76 (s, 1H),  
12 8.12 (d, 2H  $J = 8.4$  Hz).

13 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)benzoic  
14 acid (Compound 9)

15 To a solution of 58 mg (0.15 mmol) of ethyl  
16 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfoxy)benzoate  
17 (Compound 8) in 4.0 mL of tetrahydrofuran was added 1.0 mL of  
18 LiOH (2N aqueous solution) and 2.0 mL of MeOH. The solution was  
19 heated at 55 °C for 2 h and stirred at room temperature for 8 h. The  
20 reaction mixture was then concentrated in vacuo. The residue was  
21 diluted with brine and 10 % HCl and extracted with diethyl ether (2x).  
22 The combined ether layers were dried ( $\text{MgSO}_4$ ), filtered, and the  
23 solvents removed in vacuo to give the title compound as a white solid  
24 (0.39 mg, 72%):

25  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22 (s, 3H), 1.24 (s, 3H), 1.26 (s, 3H),  
26 1.29 (s, 3H), 1.66 (s, 4H), 2.34 (s, 3H), 7.10 (s, 1H), 7.70 (d, 2H  $J = 8.3$   
27 Hz), 7.76 (s, 1H), 8.17 (d, 2H,  $J = 8.3$  Hz).

28 Ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)-

1 benzoate (Compound 10)

2 To a solution of 69 mg (0.18 mmol) of ethyl  
3 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate  
4 (Compound 6) in 2.0 mL of methylene chloride was dropwise added a  
5 solution of 87 mg of m-chloroperoxybenzoic acid (0.27 mmol, 50-60%)  
6 in 2.0 mL of methylene chloride, and the resulting solution was stirred  
7 for 3 h. The reaction was diluted with water and extracted with  
8 methylene chloride (2x). The combined organic layers were dried  
9 (MgSO<sub>4</sub>), filtered, and the solvents removed in vacuo to give a white  
10 solid. The crude product was purified by flash chromatography on  
11 silica gel (9:1/hexane:ethyl acetate) to give the title compound as a  
12 white solid (51 mg, 94%):

13 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (s, 6H), 1.34 (s, 6H), 1.39 (t, 3H, J =  
14 7.1 Hz), 1.70 (s, 4H), 2.33 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 7.11 (s,  
15 1H), 7.90 (d, 2H J = 8.5 Hz), 8.15 (s & d overlapping, 3H).

16 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoic  
17 acid (Compound 11)

18 To a solution of 50 mg (0.12 mmol) of ethyl  
19 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoate  
20 (Compound 10) in 3.0 mL of tetrahydrofuran was added 1.0 mL of  
21 LiOH (1N aqueous solution). The solution was heated at 50 °C for 3 h,  
22 cooled to room temperature and concentrated in vacuo. The residue  
23 was diluted with brine, acidified using 10% HCl and extracted with  
24 ether (2x). The combined ether layers were dried (MgSO<sub>4</sub>), filtered,  
25 and the solvents were removed in vacuo to give the title compound as  
26 a white solid (45 mg, 98%):

27 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (s, 6H), 1.34 (s, 6H), 1.70 (s, 4H),  
28 2.33 (s, 3H), 7.12 (s, 1H), 7.95 (d, 2H J = 8.4 Hz), 8.15 (s, 1H), 8.22 (d,

1 2H,  $J = 8.4$  Hz).

2 Ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-  
3 nicotinate (Compound 12)

4 Sodium hydride (171 mg, 60 % dispersion in oil, 4.3 mmol) was  
5 rinsed 3 x with hexane and dried under vacuum. The vacuum was  
6 broken with dry argon and 6.6 mL of hexamethylphosphoramide  
7 (HMPA) and 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol  
8 (1.0 g, 4.27 mmol) were added sequentially. After 30 min at 50 °C,  
9 copper (I) iodide (678 mg, 3.56 mmol) was added, which caused the  
10 solution to become deep green. The solution was stirred for 15 min  
11 and ethyl 2-iodonicotinate (986 mg, 3.56 mmol) was added. The  
12 solution was heated to 90 °C for 5 h, the bath was removed, and stirring  
13 was continued overnight at room temperature. Water was added and  
14 the products were extracted with diethyl ether (3x). The combined  
15 ether layers were washed with brine, dried ( $\text{MgSO}_4$ ), filtered and the  
16 solvents removed in vacuo. The residue was purified by flash  
17 chromatography on silica gel (95:5/hexane:ethyl acetate) to give the title  
18 compound as a light yellow solid (642 mg, 47 %):

19  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.26 (s, 6H), 1.31 (s, 6H), 1.37 (t, 3H,  $J =$   
20 7.1 Hz), 1.69 (s, 4H), 2.32 (s, 3H), 4.36 (q, 2H,  $J = 7.1$  Hz), 6.68 (d,  
21 1H,  $J = 8.0$  Hz), 7.73 (s, 1H), 7.53 (s, 1H), 7.99 (dd, 1H,  $J = 2.3, 8.0$   
22 Hz), 9.00 (d, 1H,  $J = 2.3$  Hz)

23 2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinic acid  
24 (Compound 13)

25 To a solution of ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-  
26 2-naphthylthio)nicotinate (Compound 12, 300 mg, 0.78 mmol) and  
27 ethanol (8 mL) was added 2N KOH (2 mL) and the resulting solution  
28 stirred at 50 °C for 34 h. The solution was concentrated in vacuo.

1 water added, and the mixture was acidified with 10% aqueous HCl.  
2 The product was extracted with methylene chloride (3X) and the  
3 combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>),  
4 filtered and concentrated in vacuo. The solid residue was recrystallized  
5 from acetonitrile/methanol (4:1) to give the title compound (233 mg,  
6 84%) as light yellow crystals:  
7 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.21 (s, 6H), 1.26 (s, 6H), 1.63 (s, 4H),  
8 2.23 (s, 3H), 6.81 (d, 1H, J = 8.2 Hz), 7.39 (s, 1H), 7.50 (s, 1H), 7.05  
9 (dd, 1H, J = 2.1, 8.2 Hz), 8.84 (d, 1H, J = 2.1 Hz)  
10 Ethyl 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl  
11 -2-naphthylthio)-5-thiazolecarboxylate (Compound 14)  
12 Sodium hydride (0.057 g, 60% dispersion in oil, 2.4 mmol) was  
13 rinsed 3 x with hexane and dried under vacuum. The vacuum was  
14 broken and dry argon was added. To this was added 5.0 mL of  
15 hexamethylphosphoramide.  
16 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthiol (445 mg, 1.9  
17 mmol) was then added and the resulting mixture heated at 50 °C for 45  
18 min. Copper (I) iodide (0.36 g, 1.9 mmol) was added and the mixture  
19 heated at 55 °C for 1.5 h and a solution of ethyl  
20 2-iodo-5-thiazolecarboxylate (0.65 g, 2.3 mmol) in 2.0 ml of  
21 hexamethylphosphoramide was added. The mixture was heated to 95 °C  
22 for 2 h. The reaction was then cooled to 0 °C, quenched with water,  
23 and extracted with diethyl ether (2x). The organic layers were  
24 combined, washed with brine, dried (MgSO<sub>4</sub>), filtered, and the solvents  
25 were removed in vacuo. The crude product was purified by flash  
26 chromatography on silica gel (85:15/hexane:ethyl acetate) to give the  
27 title compound as an orange oil (0.30 g, 41%)  
28 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.28 (s, 6H), 1.32 (s, 6H), 1.32 (t, 3H, J =

1 7.1 Hz), 1.70 (s, 4H), 2.41 (s, 3H), 4.29 (q, 2H, J = 7.1 Hz), 7.30 (s, 1H  
2 ), 7.60 (s, 1H), 8.19 (s, 1H).

3 2-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-5-thiazolecar  
4 boxylic acid (Compound 15)

5 To a solution of 0.183 g (0.47 mmol) of ethyl  
6 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-  
7 naphthylthio)-5-thiazolecarboxylate (Compound 14) in 2.0 mL of THF  
8 was added 1.0 mL of LiOH (2.1 N aqueous solution) and 1.0 mL of  
9 MeOH. The solution was heated at 50 °C for 1 h, cooled to room  
10 temperature and concentrated in vacuo. The residue was diluted with  
11 water, the aqueous layer acidified to pH=1 using 10% HCl and  
12 extracted with ether. The combined organic layers were washed with  
13 brine, dried (MgSO<sub>4</sub>), filtered, and the solvents removed in vacuo to  
14 give the title compound as a white solid (131 mg, 78%):  
15 <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 1.28 (s, 6H), 1.32 (s, 6H), 1.73 (s, 4H),  
16 2.40 (s, 3H), 7.42 (s, 1H), 7.63 (s, 1H), 8.12 (s, 1H).

17



## 1 WHAT IS CLAIMED IS:

2 1. A compound of the formula

3

4

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6

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9

10

11 wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons.

12 or

13 X is  $[C(R_1)_2]_n$  where n is an integer between 0 and 2;14  $R_1$  is independently H or alkyl of 1 to 6 carbons;15  $R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, fluoro

16 substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or

17 alkylthio of 1 to 6 carbons;

18  $R_3$  is hydrogen, lower alkyl of 1 to 6 carbons or F;

19 m is an integer having the value of 0 - 3;

20 o is an integer having the value of 0 - 4;

21 p is an integer having the value of 0 - 2;

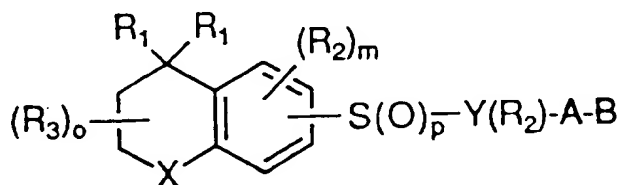
22 Y is a phenyl or naphthyl group, or heteroaryl selected from a

23 group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl,

24 pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and

25 heteroaryl groups being optionally substituted with one or two  $R_2$ 

26 groups;

27 A is  $(CH_2)_q$  where q is 0-5, lower branched chain alkyl having 3-6

1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds,  
2 and

3 B is hydrogen, COOH or a pharmaceutically acceptable salt  
4 thereof, COOR<sub>8</sub>, CONR<sub>9</sub>R<sub>10</sub>, -CH<sub>2</sub>OH, CH<sub>2</sub>OR<sub>11</sub>, CH<sub>2</sub>OCOR<sub>11</sub>, CHO,  
5 CH(OR<sub>12</sub>)<sub>2</sub>, CHOR<sub>13</sub>O, -COR<sub>7</sub>, CR<sub>7</sub>(OR<sub>12</sub>)<sub>2</sub>, CR<sub>7</sub>OR<sub>13</sub>O, or tri-lower  
6 alkylsilyl, where R<sub>7</sub> is an alkyl, cycloalkyl or alkenyl group containing 1  
7 to 5 carbons, R<sub>8</sub> is an alkyl group of 1 to 10 carbons or  
8 (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a  
9 cycloalkyl group of 5 to 10 carbons, or R<sub>8</sub> is phenyl or lower  
10 alkylphenyl, R<sub>9</sub> and R<sub>10</sub> independently are hydrogen, an alkyl group of 1  
11 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower  
12 alkylphenyl, R<sub>11</sub> is lower alkyl, phenyl or lower alkylphenyl, R<sub>12</sub> is lower  
13 alkyl, and R<sub>13</sub> is divalent alkyl radical of 2-5 carbons.

14 2. A compound in accordance with Claim 1 wherein X is  
15 [C(R<sub>1</sub>)<sub>2</sub>]<sub>n</sub> and n is 1.

16 3. A compound in accordance with Claim 1 wherein X is S.

17 4. A compound in accordance with Claim 1 wherein X is O.

18 5. A compound in accordance with Claim 1 wherein X is NR'.

19 6. A compound in accordance with Claim 1 wherein Y is  
20 phenyl.

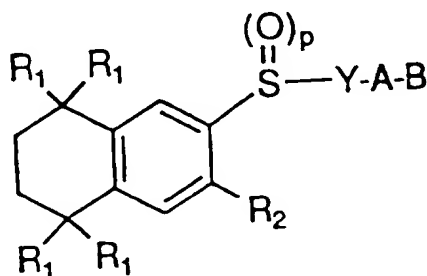
21 7. A compound in accordance with Claim 6 wherein the  
22 phenyl group is 1,4 substituted.

23 8. A compound in accordance with Claim 1 wherein Y is  
24 pyridyl.

25 9. A compound in accordance with Claim 8 wherein  
the pyridyl group is 2,5 substituted.

26 10. A compound in accordance with Claim 1 wherein Y is  
27 thiazolyl.

28 11. A compound of the formula



wherein  $R_1$  is independently H or alkyl of 1 to 6 carbons;

$R_2$  is hydrogen, lower alkyl of 1 to 6 carbons, F, or fluoro substituted alkyl of 1 to 6 carbons;

$Y$  is a phenyl or heteroaryl selected from a group consisting of pyridyl and thiazolyl;

$p$  is an integer having the value of 0 - 2;

$A$  is  $(CH_2)_q$  where  $q$  is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, and

$B$  is hydrogen, COOH or a pharmaceutically acceptable salt thereof,  $COOR_8$ ,  $CONR_9R_{10}$ ,  $-CH_2OH$ ,  $CH_2OR_{11}$ ,  $CH_2OCOR_{11}$ ,  $CHO$ ,  $CH(OR_{12})_2$ ,  $CHOR_{13}O$ ,  $-COR_7$ ,  $CR_7(OR_{12})_2$ ,  $CR_7OR_{13}O$ , or tri-lower alkylsilyl, where  $R_7$  is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons,  $R_8$  is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or  $R_8$  is phenyl or lower alkylphenyl,  $R_9$  and  $R_{10}$  independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl,  $R_{11}$  is lower alkyl, phenyl or lower alkylphenyl,  $R_{12}$  is lower alkyl, and  $R_{13}$  is divalent alkyl radical of 2-5 carbons.

12. A compound in accordance with Claim 11 wherein the  $R_1$  groups are methyl.

1           13.    A compound in accordance with Claim 12 wherein  $R_2$  is H  
2    or  $CH_3$ .

3           14.    A compound in accordance with Claim 13 wherein A is  
4     $(CH_2)_q$  where q is 0 and wherein B is COOH or a pharmaceutically  
5    acceptable salt thereof,  $COOR_8$ , or  $CONR_9R_{10}$ .

6           15.    A compound in accordance with Claim 14 wherein Y is  
7    1,4-substituted phenyl.

8           16.    A compound in accordance with Claim 15 wherein p is  
9    zero.

10          17.    A compound in accordance with Claim 16 which is ethyl  
11    4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoate,  
12    4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylthio)benzoic acid, ethyl  
13    4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoate, or  
14    4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)benzoic acid.

15          18.    A compound in accordance with Claim 15 wherein p is 1.

16          19.    A compound in accordance with Claim 18 which is ethyl  
17    4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfoxy)benzoate,  
18    ethyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsul-  
19    foxy)benzoate or 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-  
20    2-naphthylsulfoxy)benzoic acid.

21          20.    A compound in accordance with Claim 15 wherein p is 2.

22          21.    A compound in accordance with Claim 20 which is ethyl  
23    2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoate,  
24    4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylsulfonyl)benzoic acid,  
25    ethyl  
26    4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoate  
27    or  
28    4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylsulfonyl)benzoic

1 acid.

2 22. A compound in accordance with Claim 14 wherein Y is  
3 2,5-substituted pyridyl.

4 23. A compound in accordance with Claim 22 wherein p is  
5 zero.

6 24. A compound in accordance with Claim 23 which is ethyl  
7 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinate or  
8 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)nicotinic acid.

9  
10 25. A compound in accordance with Claim 14 wherein Y is  
11 2-thiazolyl substituted in the 5 position with the A-B group.

12 26. A compound in accordance with Claim 25 wherein p is  
13 zero.

14 27. A compound in accordance with Claim 26 which is ethyl  
15 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylthio)-5-thiazolecar  
16 boxylate and 2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-  
17 naphthylthio)-5-thiazolecarboxylic acid.

## INTERNATIONAL SEARCH REPORT

International Application No  
PC., US 96/17295

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 C07C323/62 C07C317/44 C07D213/80 C07D277/56 A61K31/235  
 A61K31/455 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 February 1997

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International Application No

PCT/US 96/17295

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